Remarks

Claims 1-37 are pending. Claims 1, 2, 7, 8, 11, 15, 16, 20, 21, 27, 28, 29, and 31-33 have been amended, and new claims 38-46 have been added. The specification and drawings also have been amended. Reexamination and reconsideration of the application as amended are requested. A marked-up version of the amended paragraphs and claims is attached.

Amendments to the Specification and Drawings

The specification and drawings has been amended to include a statement regarding federally sponsored research in connection with the invention. The specification and drawings have also been amended to clearly and correctly describe Figures 4, 8, 9, and 10. Formal drawings have also been prepared that incorporate the corrections needed in the informal drawings. Accordingly, a Request for Approval of Drawing Changes, along with a copy of the Formal Drawings, is submitted herewith.

Amendments to the Claims

Claims 1, 15, and 20 have been amended to specify that the microneedle has length between about 500 μm and 1 mm and a width (e.g., out diameter) between about 1 μm and 500 μm. Support for the amendment is found, for example, at page 6, lines 17-18 and 21-22, or is otherwise inherently supported by the original disclosure. See M.P.E.P. § 2163.05 (Range Limitations). Claims 1, 15, and 20 also have been amended to specify that the microneedle is perpendicular to or extends at an angle from a surface of the substrate. Support for the amendment is found, for example, at page 7, lines 1-2, and Figure 1.

Claims 7 and 8 have been amended to describe more precisely the interrelationship of the claim elements in certain embodiments of the device. Support for the amendments are found, for example, in Figure 2.

Claims 1, 2, 15, 20, 31, and 32 have been amended to eliminate the use of parenthetical labeling (e.g., (a) or (ii)) of each the elements, for clarity. Claims 2, 11, 16, 21, 27-29, and 31-33 have been amended to clarify or correct the antecedent basis of various terms, and claims 27 and 31 have been amended into dependent form. Claim 28 also has been amended use correct Markush group terminology.

New claims 38-46 have been added. Support for claims 38, 39, 42, and 43 can be found, for example, at page 5, lines 17-19. Support for claims 40 and 44 can be found, for example, at page 4, line 25 to page 5, line 7. Support for claims 41 and 45 can be found, for example, at page 7, lines 1-2. Support for claim 46 can be found, for example, at page 24, lines 25-27.

I. Rejection under 35 U.S.C. § 112

Claim 26 was rejected under 35 U.S.C. § 112, first paragraph, as non-enabled by the specification. Applicants respectfully traverse the rejection.

As taught in applicants' specification, "the amount of material flowing through the needles can be controlled by manipulating volumetric-through capacity by...filling at least some of the bores with a diffusion-limiting material" (paragraph bridging pages 27 and 28). Moreover, diffusion media, such as a gel, are also described at page 30, line 8. One of skill in the art therefore can readily select an appropriate diffusion-limiting material. Numerous types of polymeric materials, for example, are well know to serve as barriers through which other fluid

materials can diffuse at a limited rate. For example, PCT WO 00/48669, a copy of which is enclosed, describes certain types of polymeric materials that can be include within a pore (i.e. a passageway) to control the passage of liquids. It therefore would not require undue experimentation for one skilled in the art to select a material for introduction within the bore of a needle that is diffusion limiting, i.e. that will modulate the flow of a biological fluid through that conduit.

II. Rejection under 35 U.S.C. § 102

Claims 1-4, 10, 27, and 29 were rejected under 35 U.S.C. § 102(b) as anticipated by JP 07132119A to Yoshihiko (Abstract). Claims 1-4, 7,9, 12, 13, 15, 18-20, 22, 23, 25, 27, 29, 31-34, 36, and 37 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,080,116 to Erickson et al. Claims 1, 2, 10, 24, 27, 28, 30, and 36 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT WO 98/00193 to Eppstein. Claims 1, 2, 14-17, 19-21, 23, 27-28, 30-32, and 35-37 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,801,057 to Smart, et al. Claims 15-24, 31, 35, and 37 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,807,375 to Gross, et al. Applicants respectfully traverse the rejections if applied to the claims as amended.

Applicants' Claimed Devices and Methods

Applicants have developed microneedle devices for use in collecting and sensing biological fluid samples, for example, through a patient's skin. The devices include (i) a microneedle having a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm, which is perpendicular to or extends at an angle from the substrate; and (ii) a

collection chamber and/or sensor, which is/are in communication with the microneedle. In one embodiment, the microneedle of the device advantageously is sized—particularly the length—to provide a conduit through a tissue barrier such as the stratum corneum of skin to facilitate transport of a biological fluid while penetrating the skin to a sufficiently shallow depth to avoid contacting nerve endings, thereby minimizing or eliminating the pain associated with use of conventional (larger) needles for transcutaneous withdrawal and sensing of fluids. Newly developed microfabrication techniques are used to make the microneedles having a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm.

Yoshihiko

Note that a copy of an English translation of the complete published Japanese patent application is enclosed. Yoshihiko discloses a blood collecting device having hollow needles made of silicon nitride. The needles have a diameter of about 30 μm (paragraph no. 0018) and a length of 495 μm (implicit from the process description in paragraphs 0014 and 0015). There is no disclosure or suggestion of a microneedle having a length between about 500 μm and 1 mm.

Erickson

Erickson discloses a device for collecting a sample of body fluid located within the dermal layer of skin (abstract). The device includes a capillary tube disposed within a hollow needle (col. 6, lines 40-43). The needle diameter preferably has an outer diameter between .23 and .36 millimeters (col. 12, lines 64-67); however, "the preferred gauge is limited by the mechanical integrity of commercially available needles" (col. 13, lines 1-3). Erickson fails to

disclose, suggest, or enable making a microneedle having a length between about 500 μm and 1 mm, because Erickson clearly indicated his reliance on commercially available needles, which do not include those in the claimed dimensions.

"To anticipate a claim, a reference must disclose every element of the challenged claim and *enable one skilled in the art to make the anticipating subject matter.*" PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 U.S.P.Q.2d 1618, 1624 (Fed. Cir. 1996) (emphasis added); University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225, 1242 (S.D. Ind. 1995), *aff'd* 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 118 S. Ct. 1548 (1998) ("a reference cannot anticipate that which it does not enable."). It thus would require undue experimentation for the skilled artisan to produce the claimed devices in view of Erickson, because the reference discloses absolutely nothing about fabricating microneedles in the claimed dimensions.

Eppstein

Eppstein discloses a device having a plurality of puncturing members extending from a base and a plurality of holes in the base through which a liquid can move (p. 3, lines 15-30). The puncturing member is in the shape of a solid pyramid or wedge. There is no disclosure or suggestion of *hollow or porous* microneedles. Moreover, Eppstein's reservoir is not selectably in fluid communication with the puncturing member, as the puncturing member does not serve as a conduit, in contrast the applicants' hollow or porous microneedles.

Smart

Smart discloses a microsampling device that includes a hollow needle and a sampling chamber. In "the exemplary embodiment," the needle has "a length of about 3 mm." (col. 5, lines 8-11). Smart fails to disclose or suggest making a microneedle having a length between about 500 μm and 1 mm.

Gross

Gross discloses a device for transdermally delivering a liquid drug. The device includes a hollow delivery needle in communication with a drug reservoir (col. 5, lines 1-9). While Gross discloses that "the delivery and/or sensor needle(s) project outwards of the housing by 0.3-3.0 mm [300 μm to 3000 μm] and have an outer diameter of 0.05-0.4 mm [50 μm to 400 μm]" (col. 10, lines 24-26), Figure 1 discloses a delivery needle projecting 2.5 mm (col. 14, lines 52-53) and there is no description at all of the use of microfabrication techniques for manufacturing the smaller dimensioned needles. Gross therefore fails to disclose and enable the production of microneedles having a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm.

III. Rejection under 35 U.S.C. § 103

Claim 5 was rejected under 35 U.S.C. §103(a) as obvious over Erickson in view of U.S. Patent No. 5,364,374 to Morrison et al. Claim 6 was rejected under 35 U.S.C. §103(a) as obvious over Erickson in view of U.S. Patent No. 4,703,761 to Rathbone et al. Claim 8 was rejected under 35 U.S.C. §103(a) as obvious over Erickson in view of Rathbone, further in view

of U.S. Patent No. 4,664,651 to Weinshenker et al. Claims 11 and 26 were rejected under 35 U.S.C. §103(a) as obvious over Erickson in view of Gross. Applicants respectfully traverse the rejection if applied to the claims as amended.

While there is no clear motivation to combine the references, the combination still fails to disclose or suggest each and every element of the claims. The references fail to suggest or enable one of ordinary skill in the art to make microneedles in the claimed size ranges and structures.

Erickson and Morrison

As explained above, Erickson fails to disclose, suggest, or enable making a microneedle having a length between about 500 μm and 1 mm. Morrison does not supplement the deficiencies of Erickson. Morrison discloses a device for microvascular injection that includes a syringe, a blunted needle, a length of flexible tapered tubing, and a single microneedle, which is 1-5 mm long (col. 2, lines 26-36; col. 3, lines 21-22). There is no disclosure or suggestion of a microneedle having a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm.

Erickson and Rathbone

Rathbone also fails to supplement the deficiencies of Erickson. Rathbone discloses a device for taking venous blood samples that includes a needle mounted on one end of a polyethylene tube (abstract). Rathbone mentions a "23 gauge needle" (col. 5, line 45), which equates to a needle outer diameter of about *640* μm. There is no disclosure or suggestion of a

microneedle having a length between about 500 μm and 1 mm and a width between about *1 and 500* μm.

Erickson and Rathbone and Weinshenker

Weinshenker discloses an apparatus for creating a partial vacuum for use in withdrawing a blood sample from a patient. There is no disclosure or suggestion, alone or in combination with Erickson and Rathbone, of a microneedle having a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm.

Erickson and Gross

As explained above, Gross and Erickson, alone or in combination, fail to disclose and enable the production of microneedles having a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm.

IV. Other Prior Art Considered Pertinent By the Examiner

U.S. Patent No. 4,671,288 to Gough

Gough discloses an electrochemical cell sensor which comprises a "fine hollow needle" (col. 2, lines 55-57; col. 4, lines 29-32). There is no disclosure or suggestion to make microneedles that have a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm.

U.S. Patent No. 5,591,139 to Lin et al.

Lin discloses a microneedle 1-6 mm long (col. 4, lines 12-14) made in-plane in a substrate (see Figure 3). There is no disclosure or suggestion to make microneedles that have a

length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm. Moreover, there is no suggestion that one should or how one could make a microneedle of this size that is perpendicular to or extends at an angle from a surface of a substrate, because Lin teaches needles that lie in the plane of a substrate surface.

U.S. Patent No. 5,457,041 to Ginaven et al.

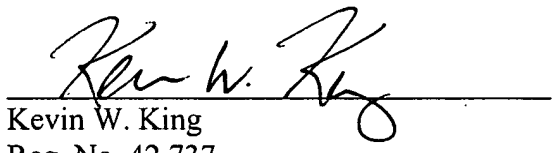
Ginaven discloses an array of solid microneedles extending from a support substrate for penetrating individual cells (abstract; col. 3, lines 29-31). The needles carry a biological substance which is transferred from the tip portions of the needles and is deposited within the target cells (abstract). There is no disclosure of fluid withdrawal or sensing. Moreover, fluid cannot be transported through a solid microneedle. There is no suggestion or enablement for making microneedles in the claimed dimensions.

Conclusion

The claims as amended are thus novel and non-obvious over the prior art of record.

Allowance of claims 1- 46 is therefore earnestly solicited.

Respectfully submitted,



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Version with Markings to Show Changes Made

To the Specification

New heading and paragraph beginning at page 1, line 7:

Statement Regarding Federally Sponsored Research

This invention was made with government support under Contract Number BES-9813321 awarded by the U.S. National Science Foundation. The government has certain rights in the invention.

Paragraph beginning at page 8, line 24:

In a preferred embodiment, the collection chamber is a standard or Luer-Lock syringe adapted to be connected to a microneedle array. See Figure 4 which illustrates a preferred embodiment wherein device **220** includes substrate **212** from which a three-dimensional array of microneedles **214** protrude. The device **220** also includes plunger **222** that is slidably secured to the upper surface of substrate **212** by plunger guide frame **224** using a restraint such as a Luer-lock interface **223**. The substrate **212** can be attached or detached to a syringe **226** via a connector such as a Luer-lock type attachment **223**. The plunger **222**, guide frame (outer syringe housing) **224**, and connector **223** connect to, form or contain reservoir [**16**] **216**. A Luer-lock type attachment alternatively may be used to secure the device to means, such as a pump, for controlling flow or transport through the device.

Paragraph beginning at page 35, line 21:

Three-dimensional arrays of microtubes were fabricated from silicon, using deep reactive ion etching combined with a modified black silicon process in a conventional reactive ion etcher. The fabrication process is illustrated in Figures 8a-d. First, arrays of 40 μm diameter circular holes **132** were patterned through photoresist **134** into a 1 μm thick SiO_2 layer **136** on a two inch

silicon wafer **138** (Figure 8a). The wafer **138** was then etched using deep reactive ion etching (DRIE) (Laermer, et al., "Bosch Deep Silicon Etching: Improving Uniformity and Etch Rate for Advanced MEMS Applications," *Micro Electro Mechanical Systems*, Orlando, Florida, USA (Jan. 17-21, 1999))[.] in an inductively coupled plasma (ICP) reactor to etch deep vertical holes **140**. The deep silicon etch was stopped after the holes **140** [are] reached approximately 200 μm deep into the silicon substrate [**38**] **138** (Figure 8b). [and the] The photoresist **134** was removed[. A], and a second photolithography step [patterned] was used to pattern the remaining SiO_2 layer **136** into circles concentric to the holes, thus leaving ring shaped oxide masks **134** surrounding the holes (Figure 8c). The photoresist **134** was then removed and the wafer **138** was again deep silicon etched, while simultaneously the holes **140** were etched completely through the wafer **138** (inside the SiO_2 ring) and the silicon was etched around the SiO_2 ring **138** leaving a cylinder **142** (Figure 8d). The resulting tubes were 150 μm in height, with an outer diameter of 80 μm, an inner diameter of 40 μm, and a tube center-to-center spacing of 300 μm.

Paragraph beginning on page 36, line 13:

Hollow metal microtubes were prepared without dry silicon etching, using a thick, photo-defined mold of epoxy. The sequences are illustrated in Figures 9a-e. First, a thick layer of SU-8 epoxy **144** was spin cast onto a silicon or glass substrate **146** that had been coated with 30 nm of titanium **148**, the sacrificial layer. Arrays of cylindrical holes **149** were then photolithographically defined through an epoxy layer **144**, typically 150 μm thick (Figure 9a). The sacrificial layer **148** at the bottom of the cylindrical holes **149** then was partially removed using a wet etching solution containing hydrofluoric acid and water [at the bottom of the cylindrical holes in the SU-8 photoresist **146**] (Figure 9b). A seed layer of Ti/Cu/Ti (30 nm/200 nm/30 nm) **139** was then conformally DC sputter-deposited onto the upper surface of the epoxy mold and onto the sidewalls of the cylindrical holes **149** (Figure 9c). As shown in Figure 9c, the seed layer **139** was electrically isolated from the substrate **146**. Subsequently, NiFe **145** was electroplated onto the seed layer **139** (Figure 9d), and the epoxy **144**, the substrate **146**, and the

sacrificial layer **148** were removed, [and was removed from the substrate 146, and the surrounding epoxy **144** was removed] leaving the electroplated structure (microtubes) consisting of the Ti/Cu/Ti seed layer **139** and the NiFe layer **145** (Figure 9e). The resulting microtubes are 200 μm in height with an outer diameter of 80 μm, an inner diameter of 60 μm, and a tube center-to-center spacing of 150 μm. The holes in the interior of the microtubes [protrude] extend through the base metal supporting the tubes.

Paragraph beginning on page 37, line 18:

Then, the upper surface of the epoxy **52** was etched away using an O_2/CHF_3 plasma until approximately 1 to 2 μm of the needle tips **51** were exposed, protruding from the epoxy **52** (Figure 10b). The silicon was then selectively removed by using a SF_6 plasma (Figure 10c). The remaining epoxy mold **52** provided a negative of the microneedles with a small diameter hole where the tip of the silicon needle protruded. After the removal of the silicon, a seed layer of Ti-Cu-Ti **54** was conformally sputter-deposited onto the top and sidewalls of the epoxy micromold **52**. Following the same process sequence as described in Example 5, NiFe **55** was then electroplated onto the seed layer **54** [(Figure 10c)]. Finally, the epoxy **52** was removed using an O_2/CHF_3 plasma, leaving a [20 x 20 array of NiFe] released structure of hollow metal microneedles **56** formed of NiFe **55** layer and Ti-Cu-Ti **54** seed layer (Figure 10d). The microneedles were made in a 20 x 20 array, and [The microneedles **56**] were 150 μm in height with a base diameter of 80 μm, a tip diameter of 10 μm, and a needle-to-needle spacing of 150 μm.

To the Claims

1. (Once amended) A device for collecting a sample of a biological fluid comprising:

[(a)] one or more hollow or porous microneedles, each having a base end and a tip, wherein the microneedle has a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm;

[(b)] a substrate to which the base of the microneedle is attached or integrated, wherein the microneedle is perpendicular to or extends at an angle from a surface of the substrate; and

[(c)] at least one collection chamber which is selectably in fluid communication with the base end of the microneedle.

2. (Once amended) The device of claim 1 further comprising [(d)] a means for inducing transport of [the] a biological fluid or component thereof into the collection chamber.

7. (Once amended) The device of claim 3 [further comprising] wherein the means for inducing transport comprises a plunger movably secured to the substrate, wherein the plunger can deform the collection chamber.

8. (Once amended) The device of claim 6 [further comprising] wherein the collection chamber comprises a one-way valve.

11. (Once amended) The device of claim 1 further comprising an adhesive material for securing the device to [the] a biological barrier surface during fluid withdrawal or sensing.

15. (Once amended) A device for sensing an analyte in a biological fluid[, the device] comprising:

[(a)] one or more microneedles, each having a base end and a tip, wherein the microneedle has a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm;

[(b)] a substrate to which the base of the microneedle is attached or integrated, wherein the microneedle is perpendicular to or extends at an angle from a surface of the substrate; and

[(c)] at least one sensor which is selectably in communication with the microneedle.

16. (Once amended) The device of claim 15 wherein the sensor comprises:

a chemical or biochemical agent that react with [the] an analyte, and

electrochemical or optical transducers which measure the reaction of the agent and the analyte.

20. (Once amended) A device for sensing an analyte in a biological fluid[, the device] comprising:

[(a)] one or more microneedles, each having a base end and a tip, wherein the microneedle has a length between about 500 μm and 1 mm and a width between about 1 μm and 500 μm; and

[(b)] a substrate to which the base of the microneedle is attached or integrated, wherein the microneedle is perpendicular to or extends at an angle from a surface of the substrate;

wherein at least one of the microneedles is or comprises a sensor.

21. (Once amended) The device of claim 20 wherein the sensor comprises:

a chemical or biochemical agent that react with [the] an analyte, and

electrochemical or optical transducers which measure the reaction of the agent and the analyte.

27. (Once amended) A method for collecting a sample of a biological fluid or analyte therein, comprising the steps:

providing [a device comprising (i) one or more hollow or porous microneedles having a base end and a tip, (ii) a substrate to which the base of the microneedle is attached or integrated, (iii) at least one collection chamber which is selectably in fluid connection with the base end of the microneedle, and (iv) a means for inducing transport of the biological fluid or component thereof into the collection chamber] the device of claim 2;

inserting the microneedles of the device into a biological barrier comprising biological fluid; and

triggering the [induction] means for inducing to permit the transport of a quantity of the biological fluid or [a component thereof] an analyte therein through the microneedles and into the collection chamber.

28. (Once amended) The method of claim 27 wherein the [induction] means for inducing is selected from the group consisting of capillary action, diffusion, mechanical pumps, electroosmosis, electrophoresis, convection, and combinations thereof.

29. (Once amended) The method of claim 27 wherein the [induction] means for inducing utilizes a pressure gradient in which the pressure within the microneedles and/or collection chamber is less than the pressure of the biological fluid adjacent the tip of the microneedle.

31. (Once amended) A method sensing an analyte in a biological fluid, comprising the steps:

[(a)] providing [a device comprising (i) one or more hollow or porous microneedles having a base end and a tip, (ii) a substrate to which the base of the microneedle is attached or integrated, and (iii) at least one sensor which is in communication with one or more of the microneedles] the device of claim 15;

[(b)] inserting the microneedles into a biological barrier comprising biological fluid which contains an analyte; and

[(c)] contacting the sensor with the biological fluid, thereby sensing the analyte.

32. (Once amended) The method of claim 31 wherein the device further comprises:

[(iv)] at least one collection chamber which is selectably in fluid connection with the base end of the microneedle, and

[(v)] a means for inducing transport of the biological fluid or component thereof into the collection chamber, [and]

wherein, after [step (b)] the microneedles are inserted, the [induction] means for inducing is triggered to draw the biological fluid or [a component thereof] an analyte therein through the microneedles and into the collection chamber.

33. (Once amended) The method of claim 32 wherein the [induction] means for inducing utilizes a pressure gradient in which the pressure within the microneedles and/or collection chamber is less than the pressure of the biological fluid adjacent the tip of the microneedle.

38. (New) The device of claim 1 wherein the microneedle comprises a metal.

39. (New) The device of claim 38 wherein the microneedle consists essentially of a metal.

40. (New) The device of claim 1 wherein the microneedle is hollow.

41. (New) The device of claim 1 wherein the microneedle is perpendicular to a surface of the substrate.

42. (New) The device of claim 15 wherein the microneedle comprises a metal.

43. (New) The device of claim 43 wherein the microneedle consists essentially of a metal.

44. (New) The device of claim 15 wherein the microneedle is hollow.

45. (New) The device of claim 15 wherein the microneedle is perpendicular to a surface of the substrate.

46. (New) The device of claim 1 wherein the microneedle has a diameter between about 40 and 120 μm.